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Short Review

RIFM fragrance ingredient safety assessment, indole, CAS Registry Number 120-72-9

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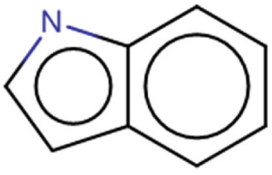
Version: 011,419. This version replaces any previous versions.

Name: Indole CAS Registry Number: 120-72-9



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. Proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic

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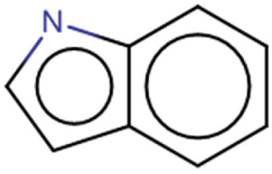

estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union

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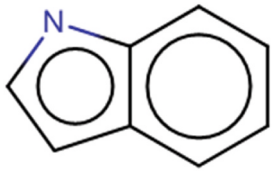

GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

Indole was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that indole is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the threshold of toxicological concern (TTC) for a Cramer Class III material, and the exposure to indole is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; indole is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; indole was found not to be persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic (Anderson, 1978; ECHA REACH Dossier: Indole; ECHA, 2017)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST.
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 101% (OECD 301B) RIFM (1993)
Bioaccumulation: Screening-level: 11.9 L/kg (EPI Suite v4.11; US EPA, 2012a)

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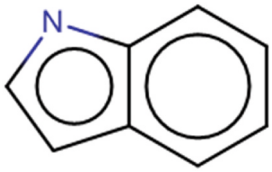

Ecotoxicity: Screening-level: 96-h Fish LC50: 2.344 mg/L (ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 96-h Fish LC50: 2.344 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.2344 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: <1

1. Identification

1. Chemical Name: Indole
2. CAS Registry Number: 120-72-9
3. Synonyms: 1-Benzazole; Benzopyrrole; 1-Benzo(b)pyrrole; 2,3-Benzopyrrole; 1H-Indole; インドール; Indole
4. Molecular Formula: C_8H_7N
5. Molecular Weight: 116.14
6. RIFM Number: 166
7. Stereochemistry: No chiral centers. No stereoisomers possible.

2. Physical data

1. **Boiling Point:** 254 °C (Fragrance Materials Association [FMA] Database), 250.04 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (FMA Database)
3. **Log K_{OW}:** 2.05 (EPI Suite)
4. **Melting Point**: 52 °C (FMA Database), 36.45 °C (EPI Suite)
5. **Water Solubility:** 1529 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.007 mm Hg 20 °C (FMA Database), 0.00684 mm Hg @ 20 °C (EPI Suite v4.0), 0.0121 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** EOA Spec. no. 21; Arctander, Volume I, 1969: White crystal flakes. Extremely diffusive and powerful odor, almost tarry-repulsive, and choking when concentrated. Concentrations lower than 0.1% shower powerful floral notes and pleasant radiation. Concentrations below 0.2 ppm have a pleasant taste, but the effect is strongly dependent upon the presence of other flavor materials and their flavor character.

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 10–100 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.02% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.000054 mg/kg/day or 0.0041 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.00040 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey,

2015, 2017; Safford, 2015a, 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015, 2017; Safford, 2015a, 2017).

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High

Expert Judgment	Toxtree v 3.1	OECD QSAR Toolbox v 3.2
III	III	III

2. Analogs Selected:
   a. Genotoxicity: None
   b. Repeated Dose Toxicity: None
   c. Reproductive Toxicity: None
   d. Skin Sensitization: None
   e. Phototoxicity/Photoallergenicity: None
   f. Local Respiratory Toxicity: None
   g. Environmental Toxicity: None
3. **Read-across Justification:** None

6. Metabolism

King (1966): Female Wistar rats (7) were administered a single dose of [2–^{14}C] indole and unlabeled indole orally as a solution in arachis oil (5%, w/v; approximately 30 mg indole). Rats were housed in a metabolic chamber through which expired air could be analyzed. Urine and feces were collected daily. After 72 h of administration, the animals were euthanized, and the radioactivity of the tissues was measured. The collected urine was evaluated for metabolites by chromatography, radioautography, and reverse isotope dilution. Chromatography studies of urine samples from rats dosed with [2–^{14}C] indole show that the major indole metabolites are 3-hydroxyindole sulfate and glucuronide, and the minor metabolites are 5-hydroxyoxindole sulfate and glucuronide, N-formylanthranilic acid, and anthranilic acid. Following oral administration, the major route of excretion is the urine (75% in 24 h; and nearly 80% in 48 h), with smaller amounts eliminated in the feces (10%) and expired air (2%). Relatively small amounts of radioactivity (0%–4% of dose) were found to remain in the tissues 2 days after dosing. These results indicate indole undergoes complete elimination. The total radioactivity in the urine constitutes indoxyl sulfate (50% of the dose), indoxyl glucuronide (11%), 5-hydroxyoxindole conjugates (3.1%), isatin (5.8%), oxindole (1.4%), and N-formylanthranilic acid (0.5%). The radioactivity in the feces included only minor components, indole (0.2% of dose) and indoxyl sulfate (0.4% of dose). Indole was also excreted through expired air as $^{14}CO_2$ (2% of the dose), which speculation that some amount of indole would have been metabolized into non-radioactive metabolites by incision of the pyrrole ring and loss of the 2–^{14}C atom. Neither indole nor any other volatile metabolite was detected in the expired air. In addition, indole is a tryptophan catabolism product and is absorbed by the human body in substantial quantities without any apparent toxicity (Gillam, 2000) (see Fig. 1).

6.1. Additional References

Posner (1961); Yasuhara (1982); Krotoszynski (1982); Holland (1984); Garcia-Regueiro (1998); Gillam (2000); Chung (1985); Eisele (1986); Stoppani (1943).

7. Natural occurrence (discrete chemical) or composition (NCS)

Indole is reported to occur in the following foods by the VCF*:

Apricot (Prunus armeniaca L.)	Coffee
Beef	Fish
Beer	Honey
Cabbage (*Brassica oleracea*)	Malt
Citrus fruits	Pork

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data. This is a partial list.

8. REACH dossier

Available; accessed 03/18/20.

9. Conclusion

The existing information supports the use of this material as described in this safety assessment.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, indole does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of indole has been evaluated in a bacterial reverse mutation assay conducted equivalent to OECD TG 471 using the pour plate method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1538 were treated with indole in dimethyl sulfoxide (DMSO) at concentrations up to 2500 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (Anderson, 1978). Under the conditions of the study, indole was not mutagenic in the Ames test.

The clastogenicity of indole was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with indole in DMSO at concentrations up to 1170 μg/mL in the dose range finding (DRF) study; the main study was conducted at concentrations up to 585 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (ECHA, 2017). Under the conditions of the study, indole was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, indole does not present a concern for genotoxic potential.

Additional References: Sasagawa (1991), Fujita (1994).

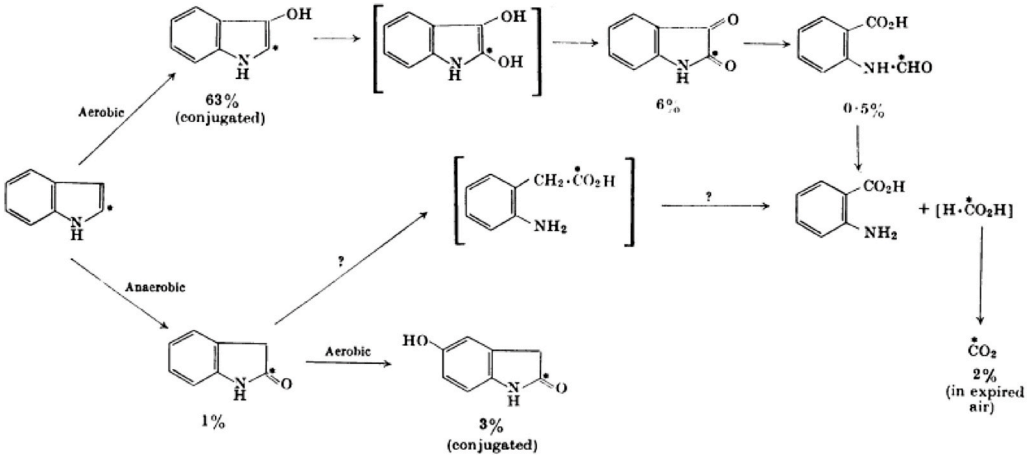

Fig. 1. The metabolism of indole (King, 1966).

Literature Search and Risk Assessment Completed On: 01/03/19.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on indole or any read-across materials. The total systemic exposure to indole is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on indole or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to indole (0.4 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: Sandage (1961a); Anderson (1989).

Literature Search and Risk Assessment Completed On: 01/07/19.

10.1.3. Reproductive toxicity

There are no reproductive toxicity data on indole or on any read-across materials. The total systemic exposure to indole is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on indole or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to indole (0.40 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/01/19.

10.1.4. Skin sensitization

Based on the existing data and the application of the DST, indole does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree 3.1.0; OECD Toolbox v4.2). No skin sensitization reactions were observed in a guinea pig open epicutaneous test (OET) (Klecak, 1985). Moreover, in a human maximization study using 1% or

Table 1
Maximum acceptable concentrations for indole that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	3.5×10^{-4}%
2	Products applied to the axillae	0.021%	0.0030%
3	Products applied to the face using fingertips	0.41%	3.1×10^{-4}%
4	Fine fragrance products	0.39%	0.020%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.0040%
6	Products with oral and lip exposure	0.23%	0.0032%
7	Products applied to the hair with some hand contact	0.79%	4.8×10^{-4}%
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.0028%
10	Household care products with mostly hand contact	2.7%	0.085%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.29%

Note: [a]For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[c]Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

690 μg/cm^2 indole, no skin reactions indicative of skin sensitization were observed in any of the 25 human volunteers. Acting conservatively, due to the insufficient data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for indole that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/06/18.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, Indole would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for indole in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of significant absorbance in the critical range, indole does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for indole were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/20/18.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for indole is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are insufficient inhalation data available on indole. Based on the Creme RIFM Model, the inhalation exposure is 0.0041 mg/day. This exposure is 114.6 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: Smyth (1962); Sgibnev (1971); Sandage (1961b); Sandage (1961a).

Literature Search and Risk Assessment Completed On: 12/11/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of indole was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, indole was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify indole as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), indole presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Key studies

10.2.1.2.1.

Biodegradation: RIFM, 1993: The ready biodegradability of the test material was evaluated using the sealed vessel test according to the OECD 301B method. After 28 days, biodegradation of 101% was observed.

10.2.1.2.2.

Ecotoxicity: No data available.

10.2.1.2.3.

Other available data: Indole has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	156.4			1000000	0.1564	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.344	3.045	3.939	10000	0.2344	Pyrazoles/Pyrroles
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	85.92	49.04	37.30			Neutral Organics

Exposure information and PEC calculation (following RIFM Framework: Salvito, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.0	2.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

Based on available data, the RQ for this material is < 1. No additional assessment is necessary.

The RIFM PNEC is 0.2344 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 01/03/19.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/31/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

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